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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,324	06/29/2001	Bi-Yu Li	1392/18/7/2	8386

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Aries A. Taylor, Jr.
JENKINS WILSON & TAYLOR P.A.
3100 Tower Boulevard
Suite 1400 University Tower
Durham, NC 27707

EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,324	LI ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on March 14, 2006 has been entered.

Status of the Application

2. Claims 1-8 are pending. Claims 1 is amended. Claims 9-23are cancelled. All amendments and arguments have been thoroughly reviewed and deemed persuasive in view of amendment. The instant amendment introduces new limitations in step (d) of the independent claims 1, that is, wherein the amplifying for no more than 25 cycles produces an amplified subset of restriction fragments that are linearly representative of the RNA population which is not present in the previously examined claims. Examiner notes that the amendment reciting linearly representative of the RNA population changed the scope of the claims to exponential PCR and overcomes the touch-down PCR, while doing so the amendment introduced new limitations as shown above and changed the scope of the independent claims to overcome the rejection under 103(a), which is based on touch-down PCR. Now the scope of the independent claim is changed, accordingly the previous rejections are withdrawn and the following new rejections have been applied to reject newly presented claims. This action is made Final, necessitated by Amendment.

New Grounds of Rejections necessitated by amendment

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ivanova et al. (Nucleic Acids Res., Vol. 23, No. 15, page 2954-2958, 1995) in view of Kato (Nucliec Acids Res., Vol. 23, No. 18, pp. 3685-3690, 1995).

Ivanova et al. teach a method of claim 1, for sequence-specific identification, separation and quantitation of an amplified subset of restriction fragments in a population of restriction fragments, wherein the method comprises

(a) reverse transcribing an RNA population to provide a double-stranded cDNA population (see page 2954, col. 2, paragraphs 1-3 under Materials and Methods section);

(b) digesting said cDNA population with one or more restriction endonucleases having cleavage sequence, wherein said restriction endonuclease is a tree to eight base cutter to produce restriction fragments having different over hangs for each restriction endonuclease (see page 2955, col. 1, line 1-2, line 1-5 under results and discussion section, col. 2, line 1-4, Fig.1);

(c) ligating said restriction fragments to adaptors lacking restriction endonucoease sites, wherein each adaptor having a sequence complementary to one of said overhangs , wherein each

ligating reaction is performed with one adapter that can be ligated to a subset of said restriction fragments (see page 2955, col. 1, line 10, col. 2, line 1-4)

(d) amplifying said subset of said restriction fragments for no more than 25 cycles with a primer comprising detectable label (biotinylated primer) , wherein primer is designed for amplifying only those restriction fragments to which said adaptors are ligated, wherein the amplification produces a linearly amplified product representative of said RNA population (see page 2955, col. 1, line 11-16, col. 2, line 1-7, page 2956, col. 1,paragraph 4, col. 2, line 1-9page 2957, col. 1, line 1-7, col.2 , paragraphs 1-2);

(e) detecting and quantifying said amplified subset of restriction fragments (see page 2955, col. 1, line 17-30, paragraph 1 under cloning section, paragraph 1 under northern bolt analysis, col. 2, line 3-18, page 2957, col. 2, paragraph 2, Fig. 4 showing the density of the fragments (quantity)).

With regard to claim 3, Ivanova et al. teach that said restriction enendonuclease comprises a four-base cutter (see page 2955, col. 1, line 1-2, page 2956, col. 1, paragraph 4).

With regard to claims 4-5Ivanova et al. teach that the method comprises further digesting the restriction fragments with one or more restriction fragments and ligating adaptors (see page 2956, col. 1, paragraph 4, col.2, line 1-9, page 2957, line 1-7, col. 2, paragraph 1;

With regard to claim s 6-8, Ivanova et al. teach that said amplification is carried out using PCR , wherein the adaptors provide priming sites for PCR , detecting and quantitating the PCR products (see page 2955, col. 1, line 6-31, page 2957, Fig. 4 showing the density of the fragments (quantity)).

However, Ivanova et al. did not specifically teach the use of restriction endonucleases having degenerate bases represented by the formula N^m..

Kato teaches a method for characterizing mRNA population using class IIS restriction fragments wherein the method comprises digesting cDNA population with one or more restriction endonucleases (see page 3686, col. 1, line 1-4) having a degenerate recognition ***or*** cleavage sequence, wherein the said restriction endonuclease is a three- to eight-base cutter which include restriction endonucleases having degenerate bases and wherein the degenerate recognition ***or*** cleavage sequence is represented by N^m where N is the extent of degeneracy (N is 2-4) and m is number of degenerate bases (m is 1-5) (restriction enzymes) produce different single stranded overhangs for each restriction endonuclease that are formed with a mixture of A, C, G, and T bases) (see page 3687, col. 1, paragraph 1 under results section, col. 2, line 1-6, page 3686, table 1), ligating adaptors amplifying said restriction fragments using adaptor primers and detecting and quantitating the amplified products using poly acrylamide gel electrophoresis and the sizes of the fragments are quantitated using sequencer (see page 3687, col, 2, line 25).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of characterizing a sub set of amplified RNA population as taught by Ivanova et al. with a step of including type-IIS restriction enzymes as taught by Kato for the purpose of enhancing the sensitivity specificity of detecting a subset of RNA population based on differential gene expression. One skilled in the art would be motivated to combine the method as taught by Ivanova et al. with the inclusion type-IIS restriction enzymes for digesting the cDNA population as taught by Kato because Kato explicitly taught that the use of type-IIS restriction enzymes for generating different restriction fragments would be

discriminate and display each expressed gene in said RNA population, reduces redundancy and provide an ideal method to generate tags for expressed genes that are used in characterizing mRNA population (see page 3685, col. 1, paragraph 3 udder introduction section, col. 2, line 1-2). . The ordinary artisan would have a reasonable expectation of success that inclusion of type IIS restriction enzymes would result in reducing the complexity and redundancy of the amplified PCR products that would enhance the sensitivity and specificity of characterizing each expressed gene in said RNA population and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Non-Statutory Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1-43 of U.S. Patent No. 6,727,068 in view of Ivanova et al. (Nucleic Acids Res., Vol. 23, No. 15, page 2954-2958, 1995) .

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1-8 are drawn to a method comprising

(a) reverse transcribing an RNA population to provide a double-stranded population;

(b) digesting said cDNA population with one or more restriction endonucleases having a degenerate recognition ***or*** cleavage sequence, wherein the said restriction endonuclease is a three- to eight-base cutter which include restriction endonucleases having degenerate bases) and wherein the degenerate recognition ***or*** cleavage sequence is represented by N^m where N is the extent of degeneracy (N is 2-4) and m is number of degenerate bases (m is 1-5) (restriction enzymes) produce different single stranded overhangs for each restriction endonuclease ;

(c) ligating said fragments to a series of adaptors lacking restriction endonuclease sites (biotinylated adaptors having degenerate bases), wherein each adaptor is cohesive to all possible overhangs;

(d) amplifying said restriction fragments;

Claims 1-8 of the instant invention fall with in the scope of the claim 1, in combination with 2-27and claim 28 in combination with 29-39, claim 40 in combination with 41-43 of the patented claims because the claims of the patent disclose said method comprising the steps (a) – (d) recited in the instant application. The only variation in the instant invention with that of the patent is that, the patented claims do not disclose amplification of restriction fragments for no more than 25 cycles.

Ivanova et al. teach a method for sequence-specific identification, separation and quantitation of an amplified subset of restriction fragments in a population of restriction fragments, wherein the method comprises

(a) reverse transcribing an RNA population to provide a double-stranded cDNA population (see page 2954, col. 2, paragraphs 1-3 under Materials and Methods section);

(b) digesting said cDNA population with one or more restriction endonucleases having cleavage sequence, wherein said restriction endonuclease is a tree to eight base cutter to produce restriction fragments having different over hangs for each restriction endonuclease (see page 2955, col. 1, line 1-2, line 1-5 under results and discussion section, col. 2, line 1-4, Fig.1);

(c) ligating said restriction fragments to adaptors lacking restriction endonucoease sites, wherein each adaptor having a sequence complementary to one of said overhangs , wherein each ligating reaction is performed with one adapter that can be ligated to a subset of said restriction fragments (see page 2955, col. 1, line 10, col. 2, line 1-4)

(d) amplifying said subset of said restriction fragments for no more than 25 cycles with a primer comprising detectable label (biotinylated primer) , wherein primer is designed for amplifying only those restriction fragments to which said adaptors are ligated , wherein the amplification produces a linearly amplified product representative of said RNA population (see page 2955, col. 1, line 11-16, col. 2, line 1-7, page 2956, col. 1,paragraph 4, col. 2, line 1-9page 2957, col. 1, line 1-7, col.2 , paragraphs 1-2).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method as taught in the patented claims with a step of including amplification for no more than 25 cycles as taught by Ivanova et al. for the purpose of enriching the amlification product exponentially . One skilled in the art would be motivated to combine the method as taught by patented claims with the inclusion amplification step with no more than 25 cycles as taught by Ivanova et al. because Ivanova et al. explicitly taught that the exponential low –stringency amplification PCR would amplify products that enable to identify and clone the fragments *(see page 2954, col. 1, abstract, paragraph 2 under introduction

section). The ordinary artisan would have a reasonable expectation of success that inclusion of amplification for no more than 25 cycles would result in enhancing the linear accumulation of amplified product that would enhance the detection of a subset of said RNA population and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Response to arguments:

5. With regard to the rejection of claims 1-8 under 35 USC 103(a) as being unpatentable over Kato et al. in view of Arbuckie, Applicants' arguments and amendment are fully considered and the rejection is withdrawn herein in view of the amendment and new grounds of rejection.

6. With regard to the rejection of claims 1-8, under provisional double patenting, (now the co-pending application is a patent) Applicants' arguments and amendment are fully considered and the rejection is withdrawn herein in view of the amendment. and new grounds of rejection.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Patent Examiner
Art Unit 1637

Prabha Chunduru
SURYAPRABHA CHUNDURU 8/30/06
PATENT EXAMINER